UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/034,950	12/26/2001	Bhami Shenoy	VPI/00-08	9344

1473 7590 02/24/2005

FISH & NEAVE IP GROUP
ROPES & GRAY LLP
1251 AVENUE OF THE AMERICAS FL C3
NEW YORK, NY 10020-1105

EXAMINER	
FETTEROLF, BRANDON J	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/034,950	SHENOY ET AL.	
	Examiner	Art Unit	
	Brandon J Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-78* is/are pending in the application.

4a) Of the above claim(s) *12,14,35-38,40-42,69,72,73,77 and 78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13,15-34,39,43-68,70,71 and 74-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

The Election filed on November 23, 2004 in response to the Response to Applicants Election filed on October 25, 2004 is acknowledged and has been entered. Applicant have elected Embodiment I, Claims 1-11, 13, 15-39, 43-68, 70-71, and 74-76, drawn to a crystal of an antibody, a composition or formulation containing a crystal of an antibody, a large batch crystallization method and a diagnostic kit, wherein said crystal of an antibody is Infliximab.

In an August 24, 2004 response to the Restriction Requirement filed on June 24, 2004, Applicant's elected with traverse Embodiment I, Claims 1-11, 13, 15-39, 43-68, 70-71, and 74-76, drawn to a crystal of an antibody, wherein the crystal is Infliximab. Applicants requested "that the Examiner reconsider the requirement for restriction between Embodiment I and Embodiment III" because the applicant believes that the claims of Embodiments I and III could be examined together without creating an undue burden on the examiner. Applicants further argued "that the claims of Embodiment I, as defined by the examiner, share common elements with the claims of Embodiment III such that they may all be combined into one group for the purposes of examination in the instant application." These arguments have been considered and are not found persuasive. MPEP 802.01 provides that restriction is proper between inventions which are independent or distinct. Here, the inventions of the various groups are distinct for the reasons set forth in the restriction requirement of June 24, 2004. Furthermore, applicants conceded that the two inventions identified, Embodiments I and III, "are identical but for differences in the specific antibody crystals claimed in claims 13 and 14." Therefore, antibodies represent materially distinct products, which differ at least in chemical structure and mechanism of action.

As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly

relevant in this art, is not coextensive and is much more important in evaluating the burden of search. Different searches and issues are involved in the examination of each group.

For these reasons the restriction requirement is deemed to be proper and is therefore made FINAL.

Claims 1-78 are currently pending.

Claims 12, 14, 40-42, 69, 72-73, and 77-78 have been withdrawn as being drawn to a non-elected invention.

Claims 35-38 have been withdrawn as being drawn to non-elected species.

Claims 1-11, 13, 15-34, 39, 43-68, 70-71, and 74-76 are currently under consideration.

Note: For examination purposes, the claims will be interpreted as reading on the elected invention Infliximab in the following manner (see specification page 98, paragraph 0272):

Claim 8 will be interpreted as reading on a crystal of a chimeric antibody. Claim 9 will be interpreted as reading on a crystal of an IgG antibody. Claim 10 will be interpreted as reading on a crystal of an IgG1 antibody. Claim 13 will be interpreted as reading on a crystal of Infliximab. Claim 15 will be interpreted as reading on a crystal of an anti-TNF antibody. Claim 16 will be interpreted as reading on a crystal of an antibody for treating an inflammatory disease.

Species Election

The response filed on August 24, 2004 to the election of a species filed on June 24, 2004 has been received. Applicants elect, with traverse, as the polymeric carrier, the species poly (amino acids) from claims 34-37 and as the ingredient, the species sucrose from claim 39 for further prosecution on the merits. Applicant did not submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. Thus, the species requirement is deemed proper.

Information Disclosure Statement

The Information Disclosure Statement filed on July 3, 2003 is acknowledged and has been considered. A signed copy of the IDS is attached hereto.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 52 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 52 recites the limitation "polyethylene glycol (PEG) concentration". However, independent claim 43 does not recite the limitation polyethylene glycol (PEG) concentration. Thus, there is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4-6, 9-11, 21-25, 31 and 33 are rejected under 35 U.S.C. 102(b) as being anticipated by Harris *et al.* (Proteins: Struct. Funct. Genet. 1995; 23: 285-289).

In the instant case, claim 1 is drawn to a crystal of a whole antibody. The crystal of a whole antibody is further drawn to wherein the antibody is: a antibody characterized by b-sheet structural content (claim 4), a therapeutic antibody (claim 5), a monoclonal antibody (claim 6), an IgG antibody (claim 9) or an IgG1 antibody (claim 10), or has a greater half-life in vivo than the soluble counterpart (claim 11). Claim 21 is drawn to a composition comprising a whole antibody crystal and at least one polymeric carrier. Claim 22 is drawn to a formulation comprising a whole antibody crystal and at least one ingredient. Claim 23 is drawn to a composition comprising a formulation comprising a whole antibody and an ingredient and at least one polymeric carrier. Claims 24-25 are drawn to a composition/formulation comprising a crystal antibody at a concentration greater than

about 1 mg/mL or greater than about 10.1 mg/mL. Claim 31 is drawn to a composition/ formulation comprising a crystal antibody wherein the crystal antibody is a therapeutic antibody. Claim 33 is drawn to wherein the polymeric carrier is a biocompatible polymer.

Harris *et al.* disclose the crystallization of intact monoclonal antibodies. Specifically, the reference teaches a crystal of an IgG1 monoclonal antibody specific for phenobarbital (abstract). Harris *et al.* further provides a composition/formulation comprising the crystalline antibody at a concentration of 8.7 mg/mL or 14.7 mg/mL, a polymeric carrier, wherein the polymeric carrier is polyethylene glycol (PEG) and at least one ingredient, wherein the ingredient is sodium citrate (page 287, Fig. 1). Thus, while Harris *et al.* do not characterize polyethylene glycol (PEG) as a polymeric carrier, the claimed limitation would be an inherent property of PEG since the specification teaches (page 21, lines 33-34) that biocompatible polymers include polyethylene glycol. Thus, the claimed polymeric carrier appears to be the same as the prior art. In addition, although the reference does not specifically teach that the crystal antibody is characterized by b-sheet structural content or its half life in vivo is greater than its soluble counterpart, the claims are drawn to the product *per se* and inherently, such a crystal antibody would have these properties. Thus, the claimed antibody crystal appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 2, 4, 6, 11, 20-24 and 32 are rejected under 35 U.S.C. 102(b) as being anticipated by Hoedemaeker *et al.* (J. Biol. Chem. 1997; 272 (47): 29784-29789).

Claim 2 is drawn to a crystal of a single-chain Fv fragment of an antibody. The crystal of a whole antibody is further drawn to wherein the antibody is: a antibody characterized by b-sheet structural content (claim 4), a monoclonal antibody (claim 6) or has a greater half-life in vivo than the soluble counterpart (claim 11). Claim 21 is drawn to a composition comprising a whole antibody crystal and at least one polymeric carrier. Claim 22 is drawn to a formulation comprising a

whole antibody crystal and at least one ingredient. Claim 23 is drawn to a composition comprising a formulation comprising a whole antibody and an ingredient and at least one polymeric carrier. Claim 24 is drawn to a composition/formulation comprising a crystal antibody at a concentration greater than about 1 mg/mL. Claim 33 is drawn to wherein the polymeric carrier is a biocompatible polymer.

Hoedemaeker *et al.* disclose a single chain Fv Fragment of P-Glycoprotein-specific monoclonal antibody C219. Specifically, the reference teaches a crystal of the anti-P-glycoprotein monoclonal antibody C219 (abstract). Hoedemaeker *et al.* further provides a composition/formulation comprising the crystalline antibody at a concentration of 7 mg/mL, a polymeric carrier, wherein the polymeric carrier is polyethylene glycol (PEG) and at least one ingredient, wherein the ingredient is sodium citrate (page 29785, 1st column, *crystallization*). Thus, while Hoedemaeker *et al.* do not characterize polyethylene glycol (PEG) as a polymeric carrier, the claimed limitation would be an inherent property of PEG since the specification teaches (page 21, lines 33-34) that biocompatible polymers include polyethylene glycol. Thus, the claimed polymeric carrier appears to be the same as the prior art. In addition, although the reference does not specifically teach that the crystal antibody is characterized by b-sheet structural content or its half life in vivo is greater than its soluble counterpart, the claims are drawn to the product *per se* and inherently, such a crystal antibody would have these properties. Thus, the claimed antibody crystal appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 1, 5, 7, 11, 19-23, 31-34, 39 and 76 are rejected under 35 U.S.C. 102(b) as being anticipated by Margolin *et al.* (IDS, WO 99/55310, 04.11.99).

In the instant case, claim 1 is drawn to a crystal of a whole antibody. The crystal of an antibody is further drawn to wherein the antibody is a therapeutic antibody (claim 5), the crystal is a carrier-free pharmaceutical controlled release crystal (claim 7), and the crystal antibody has a greater

in vivo half life compared to the soluble counterpart (claim 11). Claims 19-20 are drawn to a dried crystal of a whole antibody. Claim 21 is drawn to a composition comprising a whole antibody crystal and at least one polymeric carrier. Claim 22 is drawn to a formulation comprising a whole antibody crystal and at least one ingredient. Claim 23 is drawn to a composition comprising; (a) a formulation comprising a whole antibody crystal and an ingredient; and (b) at least one polymeric carrier. The antibody is further drawn to wherein antibody is a therapeutic antibody or antibody fragment (claim 31) or the antibody is cross linked (claim 76). The polymeric carrier is further drawn to wherein the polymeric carrier is a biodegradable polymer (claim 32), a biocompatible polymer (claim 33), a poly (amino acid) (claim 34). The ingredient is further drawn to wherein the ingredient is sucrose (claim 39).

Margolin *et al.* disclose the generation of stabilized protein crystals including, but limited to therapeutic proteins, such as antibodies, wherein the proteins molecular weight can range from proteins having a MW of 600 daltons to a glycoproteins at 1000 kilo Daltons (page 38, lines 13-15 and page 29, lines 14-25). The reference also discloses (page 9, line 26 to page 10, line 10) that the protein crystals constitute a particularly advantageous form for pharmaceutical dosage, wherein the crystals may be used for slow release in vivo. The WO application further provides compositions comprising the protein crystal and at least one polymeric carrier (page 16, lines 27-31). With regards to the polymeric carrier, the reference teaches that polymeric carriers include poly (amino acids) polymers (page 28, line 24 to page 29, line 10). Furthermore, Margolin *et al.* disclose protein crystal formulations comprising the protein crystal and at least one ingredient (page 16, lines 27-31) . With regard to the ingredient, the WIPO application that an ingredient includes, but is not limited to sweetening agents such as sucrose (page 25, line 4-8). Moreover, Margolin *et al.* teach encapsulation of protein crystal formulations in polymeric carriers to make new compositions (page 42, lines 19-25). The WIPO application also provides a method of making the protein crystals and a process by which the protein crystals are dried upon filtration of the mother liquid. In addition, the reference provides protein crystals which have been cross linked in order to slow and control the release rate (page 54, lines 17-25). Lastly, Margolin *et al.* disclose that the protein crystals can be further combined with conventional materials used in controlled release administrations, including pharmaceutical controlled release administration (page 41, lines 30-34). Although the reference does not specifically teach that the antibody crystal is a whole antibody crystal, the claims are drawn to the

product *per se* and inherently, such a protein with a molecular weight between 600 dalton to 1000 kilo Dalton can be crystallized (see specification, page 12, line 30 to page 15, line 16). Thus, the claimed antibody appears to be the same as the prior art. The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Claims 1, 3, 5, 17-18 and 70-71 are rejected under 35 U.S.C. 102(b) as being anticipated by Navia *et al.* (US 5,849,296, 1998).

In the instant case, claims 1 and 3 are drawn to a crystal of a whole antibody and a crystal of a Fab fragment of an antibody. The crystal of an antibody is further drawn to wherein the crystal antibody is a therapeutic antibody (claim 5) or a labeled antibody (claim 17). The label is further drawn to a toxin (claim 18). Claims 70 and 71 are drawn to a diagnostic kit for the in vitro detection of an antigen in a sample, wherein the antigen may be a viral antigen.

Navia *et al.* disclose crosslinked protein crystals. Specifically, the patent teaches that protein crystals of the invention include not only entire antibodies produced against a specific antigen, but also antibody fragments such as Fab fragments (column 3, lines 54-58). Moreover, Navia *et al.* disclose (column 28, lines 52-55) that the antibody crystal can be used in a diagnostic kit. For example, Navia *et al.* teach that diagnostic antibodies allow for the detection of their corresponding targets either in vivo or in vitro (column, 32, lines 15-16). Thus, while Navia *et al.* do not characterize the antigen as being a viral antigen, the claimed functional limitation would be an inherent property of the referenced method since the patent discusses (column 32, lines 8-14) an antibody may be one that binds to and inactivates viruses. Thus, it does not appear that the claim language or limitation results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-11, 13, 15-16, 19-34, 39 and 76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Margolin *et al.* (WO 99/55310, 04.11.99) as applied to claims 1, 5, 7, 11, 19-23, 31-34, 39 and 76 above, and further in view of Remicade (Remicade, Package Insert, August 1998).

Margolin *et al.* discloses, as applied to claims 1, 5, 7, 11, 19-23, 31-34, 39 and 76 above, the generation of protein crystals and composition/formulations comprising them. Specifically, the reference discloses the generation of protein crystals, wherein the protein is an antibody.

Margolin *et al.* does not teach that the antibody is Infliximab (claim 13), which is a monoclonal (claim 6), chimeric (claim 8), IgG (claim 9), IgG1 (claim 10), anti-TNF (claim 15), antibody for treating inflammatory diseases (claim 16). Furthermore, the reference does not teach that the composition or formulation has an antibody concentration greater than about 1, 10.1, 20, 50, 100, 120, or 200 mg/mL (claims 24-30)

Remicade discloses (page 1, description) infliximab as a chimeric IgG1 monoclonal antibody which is administered as a composition/formulation at a concentration of 10 mg/mL. Specifically, the package insert teaches that infliximab binds specifically to human tumor necrosis factor alpha (TNFα) and is used primarily for the treatment of inflammatory diseases.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to produce an Infliximab crystal in view of the teachings of Margolin *et al.* One would have been motivated to do so because Margolin *et al.* teaches (page 8, line 27 to page 10 line 18) that crystalline forms of biological macromolecules are advantageous for storage, large scale purification, preventing interactions which occur in solution, pharmaceutical dosage (e.g., slow release formulations in vivo), and that certain variables (e.g., crystal size, shape, formulation with excipients that effect dissolution, crosslinking) can be manipulated to produce delivery vehicles for biological molecules. Thus, one of ordinary skill in the art would have a reasonable expectation of

success that the production of an antibody crystal of infliximab in view teachings of Margolin *et al.*, one would achieve a stable infliximab crystal that can be easily purified and stored for extended periods of time. Furthermore, the claimed concentration of about 1, 10.1, 20, 50, 100, 120, or 200 mg/mL overlaps the referenced concentration of 10 mg/mL of Infliximab and is therefore an obvious variation of the reference teaching absent a showing of unobvious property. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A.

Claims 43-68 and 74-75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harris *et al.* (Proteins: Struct. Funct. Genet. 1995; 23: 285-289) in combination with McPherson (Eur. J. Biochem. 1990; 189: 1-23), and further in view of Pollock *et al.* (J. Immunol. Methods 1999;231(1-2):147-57).

In the instant case, claims 43 and 44 are drawn to a large batch crystallization method for crystallizing a whole antibody comprising the steps of: (a) mixing a solution of a whole antibody with a crystallization solution or a crystallization buffer; and (b) agitating said mixture for between about 3 and about 48 hours at a temperature between –21°C and about 61°C (claim 43), wherein the antibody is dried (claim 44). The temperature is further limited to between 4oC and about 37oC, -20oC to about 4oC, or 22oC and about 61oC (claims 45-7). The crystallization buffer is further characterized with in a range from about pH 1.9 to about a pH of 11.1, about pH 1.9 to about 4.0, about pH 3 and about pH 10 or about pH 9.0 to about pH of 11.1 (claims 48-51). The crystallization buffer further contains a polyethylene glycol concentration (w/v) between about 5 and about 40 %, about 1.9% and about 5%, about 20% or about 81% (claims 52-55). The size of the polyethylene glycol (PEG) is further characterized as ranging between about 200 and about 20000, about 200 and about 80,000, about 200 to about 400, or about 400 to about 80,000 (claims 56-59). The concentration of the antibody is further characterized as between about 0.01 mg/mL and about 500 mg/mL, about 0.01 mg/mL and about 4 mg/mL, about 10 mg/mL and about 25 mg/mL, about 3 mg/mL and about 200 mg/mL, or about 25 mg/mL and about 500 mg/mL (claims 60-64). The cyrstallizatoin buffer is further characterized as having a buffer concentration between about 10 mM and about 400 mM, about 0 mM and about 4 M, about 0mM and about 2mM, or about 1 M and about 4 M (claims 65-68). The time is further characterized as being

between 5 minutes and about 72 hours (claim 74). Claim 75 is drawn to a large batch crystallization method wherein the solution of antibody to be crystallized is produced by a method comprising: (a) centrifuging transgenic milk comprising a whole antibody to remove fat and produce skim transgenic milk; and (b) diluting the skim transgenic milk obtained in step (a) with about 250 mM EDTA to produce a solution of clarified skim transgenic milk comprising the antibody.

Harris *et al.* disclose the crystallization of intact monoclonal antibodies produced by hybridomas. Specifically, the reference teaches (page 287, Figure 1 and page 288, Table I) a method of crystallizing whole antibodies using the following conditions: (a) antibody concentration of 3-5 mg/mL; (b) polyethylene glycol (PEG) size of 3350 and concentration of 4-12 %; (c) buffer concentration of 10 mM; pH from 3.0 to 9.0; and (d) a temperature of 4, 18, 23, and 37°C.

Harris *et al.* does not teach the "optimization" of all the conditions or the time.

McPherson discloses the current approaches to macromolecular crystallization. The reference, in the instant case, conveys to one of ordinary skill in the art the knowledge that is out there in the prior art referring to the crystallization of macromolecules.

Pollock *et al.* provides a method for the production of recombinant antibodies using transgenic milk.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to optimize antibody crystallization conditions in view of the teachings of McPherson. One would have been motivated to do so because McPherson teaches that macrocrystallization is a matter of searching, as systematically as possible, the ranges of the individual parameters that impact upon crystal formation, finding a set or multiple set of these factors that yield some kind of crystals, and then optimizing the variable sets to obtain the best possible crystals (page 1, 2nd column, 3rd paragraph). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by optimizing antibody crystallization conditions in view of the teachings of McPherson, one would achieve a method of crystallizing any antibody as taught by Harris *et al.*. Further, it has been held that where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill in the art. *In re Aller*, 220 F2d 454,456,105 USPQ 233; 235 (CCPA 1955). see MPEP § 2144.05 part II A. In addition, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to produce antibodies using transgenic milk in view of the teachings of

Pollock *et al.* One would have been motivated to do so because Pollock *et al.* teaches that there is an imperative need to develop a very efficient antibody production method because therapeutic antibodies are often developed to treat clinical indications that have a large number of patients and that their effective dose is generally rather large (page 148, 1st column, 2nd paragraph). Thus, one of ordinary skill in the art would have a reasonable expectation of success that by generating antibodies by transgenic milk as taught by Pollock et al., one would achieve the ability to routinely yield mg/ml levels of antibodies as a source of large quantities of antibodies.

Therefore, NO claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached on Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeff Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner
Art Unit 1642

BF

GARY NICKOL
PRIMARY EXAMINER